8EHQ-0502-15136

211 (b) Research Group

Via Overnight Mail

NON-CONFIDENTIAL INFORMATION

May 8, 2002

TSCA Document Processing Center
U.S. Environmental Protection Agency
EPA East Bldg., Room 6428 (Mail Code 7407M)
ATTN: Document Control Officer TSCA Section 8(e)
Washington, DC 20460-0001

Re: TSCA 8(e) Submission for Clean Air Act Section 211(b) Baseline Gasoline Vapor Condensate (Lot # API 99-01)

Dear Sir/Madam:

The 211(b) Research Group (see attached membership list) is an unincorporated group of US fuel and fuel additive manufacturers affiliated by contractual obligation to meet the testing requirements of Section 211(b)(2) and 211(e) of the Clean Air Act. The 211(b) Research Group, on behalf of its member companies, is submitting this notice pursuant to TSCA Section 8(e). This notice is based upon preliminary results from a study to evaluate developmental toxicity in mice after whole-body inhalation exposure to a volatile fraction of unleaded gasoline. The findings of this study suggest that maternal exposure to the higher concentrations of this vapor condensate resulted in statistically significant reductions in litter size and fetal body weight and increased incidence of skeletal variations.

As part of the 211(b) Alternative Tier II testing program on gasoline (CAS No. 86290-81-5), a mouse whole-body inhalation developmental toxicity study was conducted. In this study, confirmed-mated mice (Crl: CD-1®(ICR) BR) were exposed to the test substance by inhalation for 6 hour/day from Gestation Day (GD) 5 through 17. Exposure levels were 0, 2000, 10,000, and 20,000 mg/m^3. Potential maternal toxicity was evaluated by clinical observations, body weight/gain, food consumption, and necropsy observations on GD 18. The uterine horns and ovaries were examined for counts of corpora lutea, implantation sites, early and late resorptions, and live and dead fetuses. Each fetus was weighed, sexed, and examined for external anomalies. Approximately one-half of the fetuses were examined for cranial and visceral anomalies; the remaining fetuses were eviscerated and stained for subsequent examination for skeletal anomalies. Anomalies were classified as malformations or variations.

The data for the toxicological parameters in this submission are attached (Tables 1 - 4). Mild maternal toxicity appeared to occur as indicated by reductions in gestation body weight and gestation body weight change in 20,000 mg/m^3 dams. The weight of the gravid uterus was also statistically reduced at this exposure level (Table 1). Mean litter size was statistically lower in the 20,000 mg/m^3 group in comparison to the control value. Normalized ratio data of resorptions/implantation sites were also statistically increased at the 20,000 mg/m^3 level compared to control suggesting some degree of fetal toxicity. These ratio data and data for live litter size may have been influenced by an entirely resorbed litter in the treated group and an

apparent difference in corpora lutea counts (14.59 vs. 12.86) between these groups (Table 2). Mean fetal body weight was statistically lower than control for both male and female fetuses at the 20,000 mg/m^3 exposure level, and for male fetuses at the 10,000 mg/m^3 level (Table 3). There were occasional statistically significant increases in visceral and skeletal variations, but no biologically or statistically significant differences from control at any exposure level with regard to pre- or post-implantation losses (%), dead fetuses, or to malformations at any exposure level (Tables 2 and 4). From the available information, the No Observable Adverse Effect Level for this study is considered to be 2000 mg/m^3.

A similar material was previously tested in a preliminary developmental study in mice. In that study, groups of 10 CD-1 mice/group were exposed to similar or slightly higher levels of a volatile fraction of gasoline vapor condensate (2653, 7960, and 23,900 mg/m^3) by inhalation for 6 hour/day from Gestation Day (GD) 6 through 17. No evidence of maternal or developmental toxicity was seen when similar maternal, reproductive and developmental endpoints, to those described for the subject study, were evaluated (API Publication Number TR 412, April 1998).

The relevance of the subject results for humans is unknown.

When the final report for this study is complete, it will be submitted to the EPA Office of Transportation and Air Quality, Transportation and Regional Programs Division, as part of the requirements of Clean Air Act Section 211(b)(2) and 211(e) (Docket No. A-90-07). If you require further information please contact me at 202-682-8344, or by mail at this address.

Regards,

Lorraine E. Twerdok

Lorraine Twerdok, Ph.D., DABT
Administrator, 211(b) Research Group

Encl - 2

cc: John Brophy, EPA
Mike Davis, EPA
Monica Alvarez, EPA
Tom Goldsworthy, ILS
Rich Schlesinger, NYU
211(b) Research Member Companies

Table 1. Mean Gestation Body Weight (g)

Exposure Level (mg/m^3)	N	GD 0	GD 5	GD 8	GD 11	GD 14	GD 17	GD 18	UTERUS	GD 18C
0	23	30.7	33.3	35.2	39.5	46.7	56.5	59.0	23.0	36.0
2,000	25	30.4	33.2	35.0	39.1	45.9	55.5	58.3	22.2	36.1
10,000	24	30.4	32.9	34.5	38.5	45.1	55.0	57.6	21.8	35.8
20,000	21	30.3	33.0	34.2	37.2*	43.5*	52.1*	54.3 *	19.1**	35.2
Stat. Analysis					AL+	AL+	AL+	AL+	A+L+	

Table 1 (cont'd). Mean Gestation Body Weight Change (g)

Exposure Level (mg/m^3)	GD 0-5	GD 5-8	GD 8-11	GD 11-14	GD 14-17	GD 17-18	GD 5-18	GD 0-18	GD 0-18C
0	2.7	1.9	4.3	7.2	9.8	2.5	25.7	28.4	5.3
2,000	2.7	1.8	4.1	6.8	6.8	2.8	25.2	27.9	5.6
10,000	2.5	1.6	4.0	6.5	9.9	2.6	24.7	27.2	5.4
20,000	2.7	1.2	3.0**	6.3	8.6	2.2	21.4**	24.0**	5.0
Stat. Analysis		L+	A+L+				A+L+	A+L+	

GD – Gestation day
C – Value corrected for uterine weight
A – Significant difference among the means, $p \leq 0.05$ (ANOVA)
A+ - Significant difference among means, $p \leq 0.01$ (ANOVA)
L+ - Response is linearly related to dose, $p \leq 0.01$ (Regression Analysis for Linear Response)
* - Mean significantly different from control mean, $p \leq 0.05$ (Dunnett's Test)
** - Mean significantly different from control mean, $p \leq 0.01$ (Dunnett's Test)

Table 2. Mean Uterine Implantation Data

Exposure Level (mg/m^3)	No. of Litters	Total Live	Live Male Fetuses	Live Female Fetuses	Resorptions	Implantation Sites	Corpora Lutea	Total Dead	Fetuses/ Implantation
0	23	13.61	7.43	6.17	0.35	14.09	14.59	0.13	0.97
2,000	25	13.52	7.12	6.40	0.56	14.16	14.60	0.08	0.96
10,000	24	13.33	6.96	6.38	0.50	14.04	14.67	0.21	0.95
20,000	22	11.0*	5.82	5.18	1.32	12.36	12.86	0.05	0.90
Stat. Analysis		A+L+	L			L	AL		

Exposure Level (mg/m^3)	Resorptions/ Implantation	Dead/ Implantation	R/I Tran	% Preimplant Loss	% Postimplant Loss	Total Malformations	Total Variations	Total Affected
0	0.02	0	10.16287	2.8	3.2	0.17	3.7	0.7
2,000	0.04	0	12.00356	3.5	4.4	0.28	4.4	0.9
10,000	0.03	0	11.19083	4.8	4.8	0.08	4.1	0.8
20,000	0.10	0	16.90805+	3.7	10.4	0.14	4.3	1.5
Stat. Analysis			KJ					

A – Significant difference among the means, $p \leq 0.05$ (ANOVA)
A+ - Significant difference among means, $p \leq 0.01$ (ANOVA)
L - Response is linearly related to dose, $p \leq 0.05$ (Regression Analysis for Linear Response)
L+ - Response is linearly related to dose, $p \leq 0.01$ (Regression Analysis for Linear Response)
K – Means differ significantly, $p \leq 0.05$ (Kruskal-Wallis Test)
J – An ordered response to the treatment levels, $p \leq 0.05$ (Jonckheere's Test)
* - Mean significantly different from control mean, $p \leq 0.05$ (Dunnett's Test)
+ - Mean significantly different from control mean, $p \leq 0.05$ (Dunn's Summed Rank Test)
R/I Tran – Resorptions/implantation sites transformed by Cohran's transformation, followed by arc sine transformation
% Preimplant loss – Pre implantation loss = (corpora lutea – implantation sites)/corpora lutea x 100
% Postimplant loss – Post implantation loss = (implantation sites – total live)/implantation sites x 100
Total affected – Total number of fetuses with resorptions, dead, or malformed/number of litters

Table 3. Mean Fetal and Litter Weights and Litter Sizes

Exposure Level (mg/m^3)	0	2,000	10,000	20,000
Mean Fetal Weight (g)				
Males	1.35	1.31	1.27*	1.28**
Females	1.29	1.26	1.22	1.24**
Mean Litter Weight (g)	18.1	17.6	16.9	14.6
Mean Litter Size	13.6	13.5	13.3	11.0*

* - Mean significantly different from control mean, $p \leq 0.05$ (Least Significant Difference)

** - Mean significantly different from control mean, $p \leq 0.01$ (Least Significant Difference)

Table 4. Fetal External, Visceral, and Skeletal Observations

Exposure Level (mg/m^3)	0	2,000	10,000	20,000
Total Fetuses with External Variations	0/313	1/338	0/320	0/212
[Total Litters with External Variations]	[0/23]	[1/25]	[0/24]	[0/21]
Total Fetuses with External Malformations	2/313	6/338	1/320	2/212
[Total Litters with External Malformations]	[2/23]	[6/25]	[1/24]	[2/21]
Total Fetuses with Visceral Variations X ++	4/155	5/167	4/159	11/122*
[Total Litters with Visceral Variations]+	[3/23]	[4/25]	[3/24]	[8/21]
Total Fetuses with Visceral Malformations	2/155	0/167	1/159	0/122
[Total Litters with Visceral Malformations]	[2/23]	[0/25]	[1/24]	[0/21]
Total Fetuses with Skeletal Variations X +	80/157	104/171	95/161	83/120**
[Total Litters with Sketal Variations]	[21/23]	[25/25]	[24/24]	[20/21]
Total Fetuses with Skeletal Malformations	0/157	2/171	0/161	1/120
[Total Litters with Skeletal Malformations]	[0/23]	[2/25]	[0/24]	[1/21]

NOTE: X $p < 0.05$ by Chi Square Analysis
* $p < 0.05$ by 2 X 2 Fisher Exact Test
** $p < 0.01$ by 2 X 2 Fisher Exact Test
\+ Dose - response trend, $p < 0.05$ by Armitage Test
++ Dose - response trend, $p < 0.01$ by Armitage Test

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